Investigating the volatilome of sandalwood powder using comprehensive two-dimensional gas chromatography coupled with time-of-flight mass spectrometry

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KEYWORDS

Sandalwood,Santalum album, Santalol, two-dimensional gas chromatography, TOF-MS, volatilome.

ABSTRACT

Sandalwood (Santalum album L.) is one of the costliest wood in the world and its characteristic aroma is highly prized in various ancient medicines for its innumerable therapeutic properties.
Although, components called α-santalol and β-santalol are primarily responsible for the evergreen fragrance of sandalwood and its many therapeutic benefits, but Sandalwood are filled with several natural chemicals that act in synergy to create a range of health-promoting effects. The presence of various volatile and non-volatile components responsible for imparting characteristic aroma and the various health benefits associated with sandalwood & its essential oils. The distribution and the ratios of these different components determine the value of the Sandalwood hence sandal wood in commercial markets is highly prone to adulteration. This study focusses on the use of two-dimensional gas chromatography coupled with time-of-flight mass spectrometry (GC×GC–TOF MS) to investigate the Sandalwood powder. This advanced analytical technique provides an increase in separation capacity to resolve the complexity of the sandalwood volatile profile and uncover components that cannot be resolved with one-dimensional GCMS techniques. Here, GC×GC–TOF MS revealed a total of 64 peaks in a sandalwood powder, tentative identifications performed against commercial mass spectral libraries. We describe how this novel approach can provide fast and accurate identification of authentic sandalwood samples with qualitative and quantitative determination of adulterants.

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1Introduction

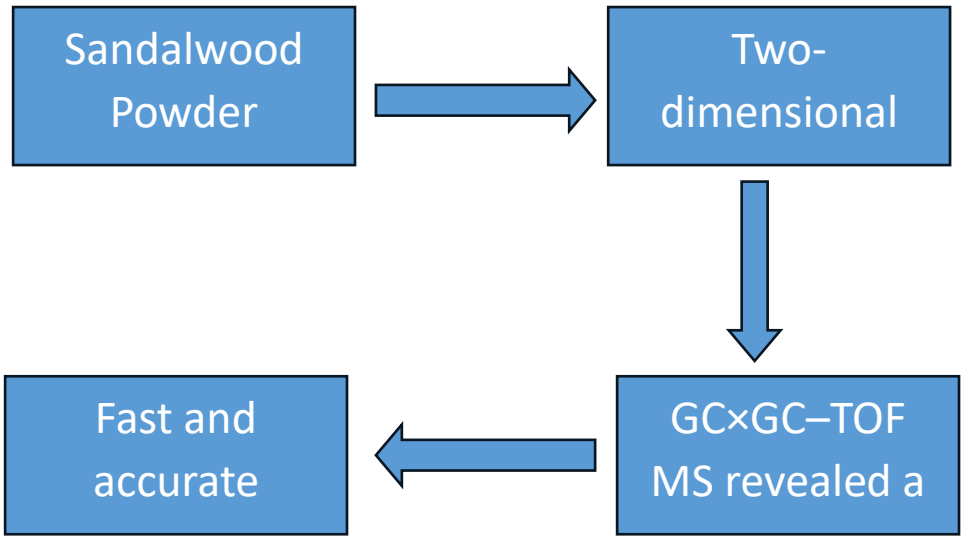
Sandalwood oil is high-value essential oil procured from the sandalwood tree – an evergreen tree which grows to a height of 5-20 m and width of 1–2.5 m. It is a semi parasitic tree, belonging to the genus *Santalum* and requiring long duration for growth (60–80 years). There are 16 different *Santalum* species with *S. spicatum* and *S. album* being most notable. The dense forests of *S. spicatum* are mostly found in Western Australia and those of *Santalum album* in southern India particularly in the state of Mysore (Pajaujis Anonis. D et al. 1998), with minor populations of these trees reported in other countries. The sandalwood tree flourishes in regions where the climate is cool with moderate rainfall, plentiful sunshine, and long periods of dry weather. The tree is planted in different states of India, but large commercial cultivation occurs in the state of Karnataka.

Sandalwood is a commercially and culturally important plant species, especially in India. It is clad by several vernacular names such as Chandan in Sanskrit and Hindi, Chandanam in Tamil and Malayalam, Gandham in Telugu and Srigandha in Kannada. The sweet, powerful, and lasting odor has made sandalwood oil useful in the perfume industry, soaps, candles, incense, folk medicine, and religious and cultural purposes for centuries. In addition, the wood and its powder are used for religious and medicinal purposes, and the food industry, especially in India (A. N. Arun Kumar et al. 2012).

Sandalwood is not only one of the most widely utilized plants in the cosmetic and perfume industry, it also has an extensive array of therapeutic properties (J.E. Brand et al. 2007). The utilization of naturally-occurring substances has been encouraged, not only due to their nontoxic behavior but also due to their capability to modulate various signaling pathways involved in the growth of multiple diseases. Sandalwood oil finds various applications in traditional medicine system of Ayurveda (Dikshit and Hussain, 1984) while the heartwood powder displays anti-bacterial (Chourasia et al., 1987) anti-remorogenic, anti-inflammatory, anti-mitotic, anti-hypertensive, anti-pyretic and sedative properties (Desai et al., 1991). Additionally, the santalols possess antiviral (Benencia et al., 1999), anti-helicobacter pylori (Takaishi et al., 2005) and anti-cancer due to apoptotic effects (Bommareddy, A et al., 2012) properties. Therapeutic effects of sandalwood powder (santalum album) in management of hyperchloesterolemic patients were also studied & it was concluded that use of sandalwood powder can prevent hyperlipidemia (Amna Rasheed et. al., 2023). The physicochemical investigations and its pharmaceutical importance of seed oil extracted from 6-year-old sandal wood plant were attempted and concluded that sandalwood seed oil isgood source of ximenynic acid and oleic acid useful to increases cellular detoxification, anti-oxidation capacity which can further be explored for value addition in the pharmaceutical and cosmetic industry (G Ravi Kumar et. al. 2019).

However, Sandalwood is one of the most expensive fragrant raw materials – in fact, its essence is often referred to as “liquid gold”. To obtain 45 liters of essential oil, approximately 1 tons of wood is required. Consequently, research is required to improve the quality and quantity of the essential oil extracted to help meet the enormous demand of the national & international market. Globally, several studies on sandalwood oil have been conducted to isolate the phytochemical components, especially both α-santalol and β-santalol, for understanding their phytochemical characters, synthesis, and pharmacological potential (Sindhu RK et al., 2017). Chemical composition of Hawaiian sandalwood oil was compared with four different santalum species originating from east India, New Caledonia, eastern Polynesia and Australia by GC & GC-MS

(Norbert A. Braun et. al. 2014).Graphical abstract highlights the analysis of sandalwood powder by using GC×GC-TOF MS resulting qualitative and quantitative determination of adulterants.



Graphical abstract: In the present experiment graphical abstract describe the analysis of sandalwood powder by using GC×GC-TOF MS.

The proportions and types of volatile compounds in sandalwood powder may vary depending on various factors like part of plant, age of plant, geographical location of plant and processing of sandalwood powder etc. Many studies have also been performed to assess the impact of geographical location on yield and chemical composition of essential oil extracted from different plant materials. India is a large country with diverse climatic conditions prevailing through different parts of the country.
Previous research indicates that there are quantitative and compositional differences in oils obtained from young and mature sandalwood trees and across heartwood sampled at different levels in the tree (Shankaranarayana and Parthasarathi, 1987). It is also noteworthy thatyields of secondary metabolites were found to be dependent on the intrinsic characteristics of plant material, environmental, and genetic aspects, as well as extrinsic aspects, such as extraction solvents used (Muzika RM et al., 1990).

Authentication of sandalwood crude drugs using gas chromatography-mass spectrometry and chemometric analysis were studied & it was concluded that S. album, the correct species mentioned for medicinal use of sandalwood was currently substituted with other santalum species (Sununta Srisopon et. al., 2019).

Evaluation of chemical and physical properties of commercial sandalwood essential oils and their comparison with essential oil extracted from Santalum album L were studied in detail &based on research outcome it was recommended that authentication for high valued

sandalwood essential oil should mainly rely on its physical (RI & RD) and chemical analysis (level of α – and β– santalol content) (S.S. Bisht. et.al 2020). Simple and rapid infra-red (IR) spectrum based detection method for discrimination of pure sandalwood and other essential oils were studied & patented (S.S. Bisht. et.al 2020), further phytochemical investigation of fruit,seed, bark, leaf, stem and root of Indian sandalwood and their potential adulterants or substitutes of the sandal wood and its oil were studied (S.S. Bisht. et.al 2021).

GC×GC has previously been applied to the analysis of west Australian sandalwood oil, where a total of 8 characteristic components of santalum spicatum essential oil were sufficiently well resolved to enable their quantitation by flame ionization detection (FID) (Robert Shellie. et. al. 2004). The complex nature of such essential oils makes quantitative analysis by conventional GC–FID more challenging.Evaluation of the quality of sandalwood essential oil is often performed by gas chromatography-mass spectrometry (GC-MS) (Melanie-Jayne R. Howes et al. 2004). Rapid, routine, cost effective, quantitative and qualitative screening of sesquiterpenoids in sandal wood essential oil by High Performance Thin Layer Chromatography (HPTLC)& its comparative analysis by GC were evaluated in which total 16 and 9 major constituents of sandalwood oil by GC & HPTLC respectively were well resolved (Biswapriya B. Misra et al., 2013). Further, a total of 46 constituents composed of a great variety of n-alkanes, sesquiterpenoids, fatty acids, aldehydes, naphthalene derivatives, methyl esters, alcohols, carotenoid degradation products, and acetates were identified using Gas chromatography ion trap quadruple mass spectrometry in volatile profiling of sandalwood heartwood oil (Biswapriya B. Misra et al., 2013). However, there is much that remains unknown about the composition of both Sandalwood oils and powders.

Comprehensive two-dimensional gas chromatography coupled with time-of-flight mass spectrometry (2D GC×GC-TOFMS) offers enhanced separation to reveal greater component detail and gain better understanding of the factors affecting Sandalwood composition. GC×GC technique uses two columns of different selectivity which allows orthogonal separation mechanisms to provide a second dimension of sample separation and therefore the ability to reveal ‘hidden’ analytes that otherwise unresolved on a single column.This novel, rapid, precise, convenient &advanced hyphenated analytical technique i.e. 2D GC×GC–TOFMS was usedfirst time to increase the separation capacity to resolve the complexity of the volatile profile of sandalwood powder and uncover components that cannot be resolved with one dimensional gas chromatography-mass spectrometry & have not previously been reported based on spectral matches with NIST Risk Management Framework (RMF) greater than 700 in commercial mass spectral libraries, including the National Institute of Standards and Technology (NIST) 2017 library and the Wiley Registry (12th Edition).

Method and Materials

Sample: Sandalwood powder was obtained from M/S Hamdard Laboratories (India) and 40 mg was dissolved in 1 mL of dichloromethane. As four solvents i.e. n-hexane, n-pentane, diethyl ether and ethyl acetate were already used for extraction, detection and quantify fourteen major sesquiterpenoids from immature heartwood by gas chromatography-mass spectrometry method employing an ion trap quadrupole (ITQ) mass analyzer (Biswapriya B. Misra et al., 2012).

GC×GC: A non-polar to polar column setup was utilised to separate components based on both volatility and polarity. Separation was performed on the Agilent 7890B gas chromatograph

utilising the following columns: 1D: BPX5 – 20 m × 0.18 mm i.d. × 0.18 µm film thickness and 2D: BPX90 – 5 m × 0.25 mm id. × 0.25 µm film thickness. Oven temperature was 60°C (1 min), 7°C/min to 320°C (0 min), 1°C/min to 330°C (15 min). The INSIGHT®-Flow modulator (SepSolve Analytical, Peterborough, UK) was used to provide reverse fill/flush flow modulation, with a 25 µL sample loop and a bleed line of 5 m × 0.1 mm i.d. The modulation period was 3.5 seconds, with a flush time of 80 ms.
Parallel detection was utilized between FID and TOF MS in a ratio of 5: 1.
FID: Temperature of 300º C with air flow of 300 mL/min. The H_2 fuel flow was 10 mL/min and N_2 flow (as the makeup gas) was 5 mL/min.
TOF MS: A BenchTOF time-of-flight mass spectrometer (SepSolve Analytical, Peterborough, UK) was used with an ion source temperature of 300ºC and transfer line temperature of 300ºC. The filament voltage was 1.8 V and the ionization energy was 70 eV. The mass range was m/z 35-500, with the TOF simultaneously analysing all ions in the mass range.
Data analysis: ChromSpace® software (SepSolve Analytical, Peterborough, UK) was used for both acquisition and post-analysis data processing. The chromatogram was deconvolved, integrated and mass spectra searched against commercial mass spectral libraries, including the National Institute of Standards and Technology (NIST) 2017 library and the Wiley Registry (12th Edition), for tentative identification based on both mass spectral match factor and retention indices.

Results & discussion

A sandalwood powder was analysed using GC×GC-TOF MS resulting in the two-dimensional color plot displayed in Figure 1. GCxGC has much higher peak capacity, better detectability due to the analytes refocusing in the modulator & obtain structured chromatograms which in turn facilitate recognition of unknowns than conventional 1D GC. For the analysis of the sandalwood powder, a non-polar to polar column configuration was utilized to separate the constituents by both volatilities in the first dimension and polarity in the second dimension. This configuration ensures that any solvent tail and column bleed will elute as a distinct band early in the second dimension well separated from other compounds of interest.

In current study of sandalwood powder sample using comprehensive two-dimensional gas chromatography coupled with time-of-flight mass spectrometry, A total of 64 peaks were then tentatively identified (Table-1) based on spectral matches to commercial mass spectral libraries including the National Institute of Standards and Technology (NIST) 2017 library and the Wiley Registry (12th Edition), out of 64 peaks, 42 compounds were tentatively identifiedbased on spectral matches with NIST Risk Management Framework (RMF) greater than 700. The curated list of the identified compounds is presented in the Table-1. As seen in the curated peak table-1, the most abundant peaks are cis-α-Santalol and trans-β-Santalol. The santalol isomers are sesquiterpenes that comprise 70–90% of sandalwood oil, which is found in the heartwood of the tropical tree Santalum album and other members of that genus. The fragrant oil is valued as a component in perfumes. 39 volatile components were identified from S. album mainly olefins,olefins like Santalene epi-beta-, Santalene, beta-Santalene & Santene make the material firm, not easy to break and aroma stronger during the burning process (Gutong Chen et. al, 2020).Teresantalol belongs to the class of organic compounds known as bicyclic monoterpenoids containing exactly 2 rings, which are fused to each other. Santalal isomers are flavoring

Table 1: Table 1: Compounds identified in Sandalwood powder sample using GC×GC-TOF MS.

Peak No.	Compound	Match factor	RI	1tR (min)	2tR (s)	Peak area	Area %	Odour description and comments
1	trans-β-Ocimene	792	1049	15.1006	1.8351	4.32E+05	0.23	Tropical, green, terpy, woody
2	Butanone, 3,3-diacetoxy-		1066	15.6649	4.3215	1.69E+06	0.92	
3	Santene	811		15.8083	1.9307	1.24E+05	0.07	
4	Tricycloekasantalal	929	1343	17.3163	1.8781	7.66E+05	0.41	
5	Acetaldehyde, 2-(alpha-pinen-8-yl)-	810		17.5243	1.8627	1.13E+05	0.06	
6	exo-eka-tricylcosantalal	836	1385	18.1417	1.9839	1.38E+05	0.07	
7	p-Cymen-9-ol, acetate	773	1415	18.4917	2.3148	3.18E+04	0.02	
8	**Unknown peak - teresantalol derivative**			18.9583	1.4434	5.44E+04	0.03	
9	Santalene, epi-beta-	852	1441	19.1917	1.4204	7.18E+04	0.04	
10	Santalene, beta-	796	1453	19.4016	1.4175	9.35E+04	0.05	Woody
11	α-Curcumene	835	1468	19.7167	1.5387	7.01E+04	0.04	Herbal
12	Benzoic acid, 4-ethoxy-, ethyl ester	751	1522	20.1000	2.6399	2.86E+04	0.02	
13	**Unknown teresantalol derivative**			20.4289	1.6192	6.31E+04	0.03	
14	**Unknown teresantalol derivative**			20.5017	1.8944	9.52E+04	0.05	
15	Buten-2-ol, 2-methyl-4-teresantalyl-3-	774		20.9531	1.9871	1.34E+05	0.07	
16	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	890	1588	21.1641	1.5554	1.16E+06	0.63	
17	**Unknown teresantalol derivative**	864		21.3539	1.9887	8.56E+05	0.46	
18	Diethyl Phthalate	955	1594	21.4345	3.1556	8.35E+06	4.51	
19	**Unknown**			21.9333	2.0775	5.39E+05	0.29	

	teresantalol derivative							
20	1-((1S,3aR,4S,7R,7aR)-3a,7a-Dimethyloctahydro-1H-4,7-methanoinden-1-yl)ethanone	790	1589	22.0747	1.9662	3.41E+05	0.18	
21	**Unknown teresantalol derivative**	827		22.4411	1.9555	3.67E+05	0.20	
22	**Unknown**			22.6015	3.8511	1.14E+06	0.62	
23	cis-α-Santalal	830		23.0884	1.8519	1.17E+06	0.63	
24	**Unknown C16H24 isomer**			23.1677	2.0446	6.23E+05	0.34	
25	cis-α-Santalol	930	1680	23.2907	2.3768	4.62E+07	25.00	Woody
26	cis-α-Santalal	850	1648	23.3776	1.9248	3.48E+06	1.88	
27	α-Santalyl formate	803	1728	23.7417	1.8377	1.62E+05	0.09	Woody dry oily floral
28	beta-Santalol	915	1716	23.9988	2.4729	2.32E+07	12.52	
29	Naphthalene, 2,6-diisopropyl-	721	1728	24.0917	1.9169	2.76E+04	0.01	faint sweet odour
30	**Unknown santalal isomer**	824		24.0917	2.0092	6.78E+05	0.37	
31	Nuciferol, cis-	898	1729	24.1371	2.8228	1.39E+06	0.75	
32	Lanceol, cis-	863	1763	24.6931	2.4770	3.41E+06	1.84	
33	Spirosantalol	854		24.6949	2.7845	4.03E+05	0.22	
34	**Unknown santalol isomer**			25.3167	1.7922	5.93E+04	0.03	
35	Ethane, 1,2-diphenoxy-	898	1811	25.3361	3.1036	5.94E+05	0.32	
36	Diisobutyl phthalate	958	1827	25.9000	2.3187	8.02E+05	0.43	
37	Methyl hexadecanoate	887		26.6000	1.4863	3.91E+04	0.02	
38	**Unknown**	717		26.7167	1.6530	1.92E+05	0.10	
39	Dibutyl phthalate	954	1914	27.3085	2.4308	2.81E+05	0.15	
40	**Unknown santalol derivative**			26.7167	1.6530	1.92E+05	0.10	
41	Benzoic acid, 2-benzoyl-, methyl ester	864		27.3583	4.2167	8.14E+04	0.04	
42	Naphthalene, 1-(phenylmethoxy)-	865		30.6833	3.4849	6.10E+04	0.03	
43	Santalol acetate	719	1867	31.5338	2.0067	5.58E+05	0.30	

44	Bis(2-ethylhexyl) phthalate	818	2535	34.4750	1.9495	7.39E+04	0.04	
45	**Unknown**			37.0101	1.5811	3.47E+05	0.19	
46	**Unknown santalol derivative**			37.2230	1.8012	1.27E+06	0.69	
47	Squalene	704	2827	37.3160	1.4602	3.91E+05	0.21	
48	α-Santalol derivative (similar to α-Santalol linoleoate)			37.7123	2.8337	1.87E+07	10.11	
49	Cholest-3-ene, (5α)-	875		37.7417	1.6356	2.91E+06	1.57	
50	Cholestan-3-ol, acetate, (3β,5α)-	796		38.0333	1.6546	1.29E+06	0.70	
51	α-Santalyl palmitate	746	3190	38.0755	2.5952	6.64E+05	0.36	
52	**Unknown santalol derivative**			38.3505	2.8806	8.66E+05	0.47	
53	**Unknown santalol derivative**			38.4511	3.0945	1.20E+06	0.65	
54	**Unknown β-Santalol derivative**			38.5939	2.8837	6.90E+06	3.73	
55	β-Amyrin	665	3295	39.0217	1.2070	1.28E+06	0.69	
56	**Unknown**			39.0073	2.7580	2.00E+05	0.11	
57	**Unknown**			39.1350	1.7167	2.86E+05	0.15	
58	**Unknown α-Santalyl palmitate isomer**			41.4618	1.9720	1.16E+07	6.27	
59	β-Santalol, palmitate	754		42.0131	2.1018	4.57E+06	2.47	
60	α-Santalol derivative (similar to α-Santalol linoleoate)			44.0288	2.3977	1.77E+07	9.59	
61	**Unknown α-Santalyl palmitate isomer**			44.2750	2.3132	8.10E+05	0.44	
62	**Unknown santalol derivative**			44.5667	2.7661	1.50E+06	0.81	
63	**Unknown santalol derivative**			44.6958	2.5779	6.92E+06	3.74	
64	β-Amyrone	789		45.3923	4.0870	5.22E+06	2.82	

ingredient belongs to the class of organic compounds known as sesquiterpenoids. These are terpenes with three consecutive isoprene units.These compounds are thought to contribute to the woody aroma of the sandalwood powder. Throughout the chromatogram there are several unidentified peaks which exhibit very similar spectra sharing m/z 43, 79, 91 and 121 ions. These peaks are displayed as 'Unknown Peak*' in the peak table. These detected compounds did not provide a strong hit against our available libraries; however, a more populated fragrance library

is likely to enable identification of these compounds.Table 1 highlight the compounds identified in sandalwood powder sample using GC×GC-TOF MS where as GC×GC-TOF MS color plot of the sandalwood powder dissolved in dichloromethane, with the two major constituents highlighted (A) α-Santalol and (B) β-Santalol.

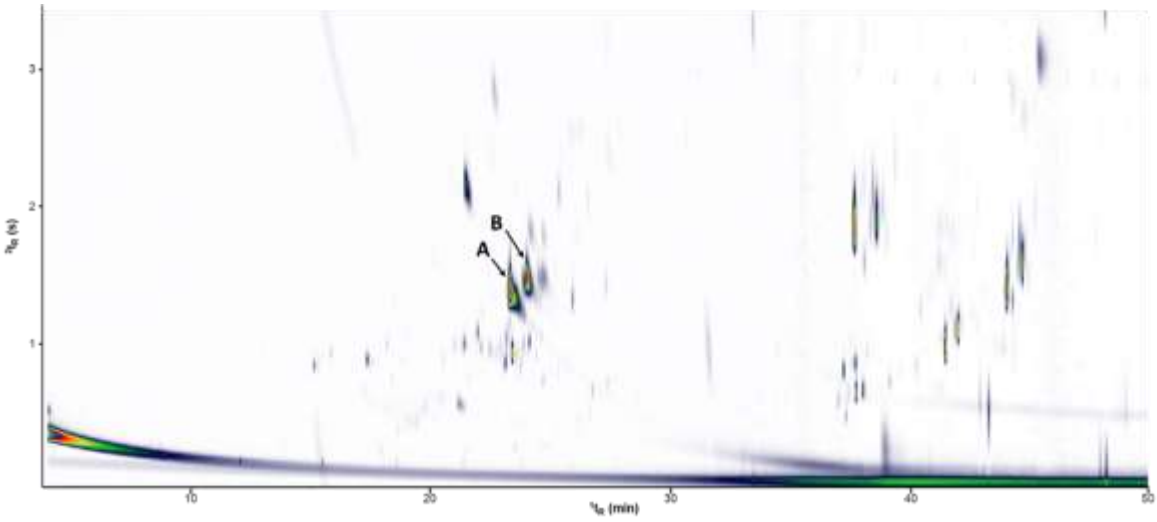


Figure-1GC×GC-TOF MScolor plot of the sandalwood powder dissolved in dichloromethane, with the two major constituents highlighted (A) α-Santalol and (B) β-Santalol.

Conclusion

Complexities of constituents, similarities in mass spectra with reduced resolution and peak capacity and difficulties in peak identification have made GC×GC–TOF MS a popular choice for complex natural products and volatilome of essential oils analysis. To the authors' knowledge, this is the first study to utilize GC×GC-TOF MS for the analysis of sandalwood powder, enabling previously unreported compounds to be identified.The accurate and rapid identification of the sandalwood powder for cis-α-Santalol and trans-β-Santalol, as well astheir isomers, mayprove useful for quality control analysis of sandalwood samples for medicinal use. Furthermore, the compounds reported may lead to the discovery of novel phytopharmaceuticals from sandalwood tree. The manuscript thus demonstrates that with the use of cutting-edge technology better results can be obtained by developing protocols which are quick and precise. The study recommends the exploitation of GC×GC–TOF MS to detect sandalwood timber adulterants.Advance in the technologies of ionization, ion detection as well as high speed signal and data processing make GC×GC–TOF MS an attractive alternative to conventional mass

analysers for qualitative and quantitative analysis of volatile constituents from heartwood of the sandalwood tree.

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